EXHIBIT B

Meinwald Report's rebuttal of MacMillan Report

MacMillan Report	Rebuttal in Meinwald Report
¶57: "*Oxidizing* means combining with oxygen, and in this case, specifically involves an oxidation reaction in which oxygen is combined with a pro-chiral sulfide (such as the omeprazole sulfide). . . . An *oxidizing agent* means a substance that readily transfers oxygen atoms. Even more generally, an oxidizing agent readily accepts one or more electrons from the substance being oxidized, in an oxidation reaction. 'Cumene hydroperoxide' is an example of an oxidizing agent." ¶64: Definitions of *oxidizing* and *oxidizing agent* repeated. ¶65: "Oxygen atoms from an oxidizing agent are typically highly reactive."	¶¶45-47, 49: "[I]n my opinion, Dr. MacMillan's characterizations of the meaning of the terms *oxidizing* and *oxidizing* agent are fundamentally flawed. Dr. MacMillan writes in paragraph 57: "*Oxidizing means combining with oxygen*, and in this case specifically involves an oxidation reaction in which oxygen is combined with a pro-chiral sulfide (such as the omeprazole sulfide)." Whereas the transformation of a sulfide to a sulfoxide is certainly a good example of one type of oxidation which does actually involve the transfer of an oxygen atom, there are countless examples of reactions in which oxygen atoms are transferred which are not generally considered as oxidations. . . . In addition, many *bona fide* oxidations do not involve oxygen transfer at all . . . . MacMillan's definition of *oxidizing agent* is similarly confusing. MacMillan writes: "An *oxidizing agent* means a substance that readily transfers oxygen atoms." However, this is clearly not true for the reaction between sodium and chlorine to produce sodium chloride (table salt), which a POSA would recognize to involve chlorine as an oxidizing agent. . . . MacMillan's paragraph 64 repeats the only partially correct definitions of *oxidizing* and *oxidizing agent* previously discussed. Paragraph 65's statement that "Oxygen atoms from an oxidizing agent are typically highly reactive" is ambiguous, and its relevance to the subject under consideration is unclear."
¶61: "Enantioselective, or "asymmetric," oxidation therefore requires special kinds of helper molecules and chemical associations that orient the reactant (such as the	¶48: "MacMillan's paragraph 61 gives a somewhat misleading description of "Enantiospecific, or asymmetric," oxidation, of which it is said that it "requires special kinds of

MacMillan Report	Rebuttal in Meinwald Report
omeprazole sulfide) in space in a way that makes its interactions with other molecules more likely to occur in one direction than another."	helper molecules and chemical associations that *orient the reactant (such as omeprazole sulfide) in space* in a way that makes its interactions with other molecules more likely to occur in one direction than another." This seems to imply that the "helper" holds the reactant (omeprazole sulfide) in some sort of preferable position in space (or perhaps in the solvent in which the oxidation occurs). This freezing of a molecule into one orientation in solution is hardly possible, since molecules in solution are known to tumble rapidly. A more accurate description might be that the asymmetric helper binds or interacts with the reactant (or the oxidizing agent) in such a way that delivery of the oxygen atom is more likely to occur from one direction than another."
¶79: "Nowhere in Dr. Pitchen's synthetic scheme did he or any of his coworkers ever mention trying to prepare a different chiral titanium complex, or to prepare it under different conditions than those employed by Dr. Kagan himself. Even though multiple, tedious chemical steps might be avoided with a more effective and efficient chiral titanium complex, Dr. Pitchen did not attempt any modifications of the Kagan chiral titanium complex. Given the almost identical nature of the substituents in the Pitchen case (electronics as well as functional groups that will interact with the complex, particularly nitrogen and N-H systems), it is apparent that Dr. Pitchen had no idea how to prepare a chiral titanium complex that could yield anything more than a racemic mixture."	¶50: "In paragraph 79, Dr. MacMillan stresses that Dr. Pitchen "did not attempt any modification of the Kagan chiral titanium complex." He claims "Dr. Pitchen had no idea how to prepare a chiral titanium complex that could yield anything more than a racemic mixture." We cannot know what ideas were or weren't in Dr. Pitchen's mind, but we do know that he was clearly able to bring about oxidation of several sulfides to chiral sulfoxides significantly enriched in one enantiomer by the use of Kagan's catalyst."
¶81: "Rather, the term *chiral titanium complex* of claims 2-4, as understood by one of ordinary skill in the art, takes account not only of the chiral ligand (such as diethyl	¶¶51-52: "In paragraph 81, Dr. MacMillan makes the case that the *chiral titanium complex* described in the '789 patent "is different than that of Kagan" even though both are made from

MacMillan Report	Rebuttal in Meinwald Report
tartrate), titanium compound (such as titanium isopropoxide), and water, but also accounts for factors such as other components and conditions, including but not limited to: 1) what other components may be included in the complex or associated with the complex; 2) how the complex was prepared; 3) to what substrates the complex may reasonably be applied; and 4) under what range of conditions it will confer enantioselectivity. The '789 patent demonstrates that these factors produce a complex that is different than that of Kagan."	"the chiral ligand (such as diethyl tartrate), titanium compound (such as titanium isopropoxide) and water." While it is obviously true that fine tuning of the Kagan/Pitchen procedure was described in the '789 patent, what is remarkable is that the patent in fact specifies the *very same key components, titanium isopropoxide, diethyl tartrate, and water* as those specified earlier (in several 1984 and 1987 publications) by Kagan. . . . In fact, the Kagan catalyst itself is very similar to the catalyst described even earlier by Sharpless (1980-1984) for accomplishing the enantioselective epoxidation of allylic alcohols. While Sharpless' discovery that titanium isopropoxide and diethyl tartrate catalyzed the oxidation of allylic alcohols by t-butylhydroperoxide, Kagan found that in the case of oxidizing a sulfide to the corresponding sulfoxide, the addition of water to these two components as the final step in catalyst production was necessary to produce a version of the Sharpless catalyst able to bring about the desired stereoselective delivery of an oxygen atom to a sulfide in order to produce the corresponding sulfoxide enantioselectively. In my opinion, no POSA would see the `789 patent catalyst complex to be original or inventive, since the use of its key components was already well described."
¶83: "In my opinion, one of ordinary skill in the art would understand, therefore, that when the '789 patent discusses "order of addition" relative to the prior art, the implication is one of time, rather than sequence."	¶53: "In paragraph 83, Dr. MacMillan tells us that the '789 patent's discussion of "order of addition" is not a reference to the *sequence* in which components are added, but rather that "the implication is one of *time*." This is certainly a non-standard reading of the term "order," which usually does specify a sequence, as in the term "alphabetical order," or the sequence of musical notes in a tune. To lengthen or shorten the time duration of any of the notes in a melody would certainly distort its character a bit, but to change the order of the notes would mean to play them in a different sequence and would change the tune in a way

MacMillan Report	Rebuttal in Meinwald Report
	that would have nothing to do with how long each note is held. Depending on the nature of the change, the result would be a clearly altered tune. In my opinion, "order of addition" has nothing at all to do with *time*, and everything to do with a *sequence* of actions or steps."
¶110: "To be more specific, when I analyzed the AstraZeneca Complex as prepared using the conditions of the '789 patent and the prior art Kagan Complex using two different types of NMR, I observed distinct peaks at about 3.75 and 70 ppm in the ^{1}H NMR and ^{13}C NMR, respectively, using the AstraZeneca conditions, but not the Kagan conditions."	¶54: "In his paragraph 110, Dr. MacMillan makes the case that the catalyst complex for sulfide oxidation he has prepared in his own laboratories according to the AstraZeneca '789 patent instructions is different from Kagan's complex, as evidenced by the spectroscopic presence of distinct additional peaks in its 1H and 13C NMR spectra at 3.75 and 70 ppm respectively. These are not seen in the spectra of Kagan's catalyst. While a difference in the NMR spectra of two samples is evidence of a difference in composition of these samples, a chemist would want to know what these additional spectroscopic "peaks" are attributable to. This information does not seem to be disclosed in his report. These two samples are relatively complex mixtures of components, not all of which are necessarily associated with the desired catalytic activity. It is perfectly possible that the additional peaks belong to a component that is an impurity in the AstraZeneca catalyst that is not present in the Kagan catalyst. This additional component might be catalytic, or it might be inert. In my view, it is impossible to ascribe any significance to these spectroscopic observations without knowing what proton(s) and carbon atom(s) in what chemical species they represent, and whether this additional species is actually involved in the catalytic mechanism in some beneficial way."